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A facile synthetic approach for the syntheses of 7-hydroxyflavonol derivatives

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ABSTRACT

Present synthetic method represents the synthesis of 7-hydroxyflavonols in fewer reaction time, with high purity and good yields. By this one-step synthetic technique various 7-hydroxyflavonols derivatives were prepared. This improved method shows a high impact in synthetic methodology with compare to previously reported many step, low yield and longtime reaction methods.

Keywords: 7-Hydroxyflavonols, Synthetic Methodology, High Purity.

INTRODUCTION

Flavonols are a key class of flavonoids having 3-hydroxyflavone backbone. They are composed of fused phenyl (A) and pyranyl (C) rings, and a phenyl (B) ring attached with pyranyl (C) ring. Flavonoids are polyphenolic compounds, which exist in numerous plants, vegetables as well as in fruits. Their intake is estimated about 20-50 mg per day in the humans which differs as per diet consumed. Flavonoids Shows CYP (P450) activity, and this Flavonols class inhibits CYP3A4[1] and CYP2C9[2] enzymes, which are responsible for the metabolism of drugs in the human body. This class has displayed significant pharmacological and biological activities as antioxidant, anticancer, antimicrobial, anti-inflammatory and immune responses[3–7]. These flavonoids easily form stable chelates with various metals due to presence of hydroxyl groups and carbonyl functional groups [8,9] and many natural flavonoids like quercetin, luteolin, catechin, cyaniding are having an o-dihydroxyl groups in the phenyl ring B which provides another chelating site[10].

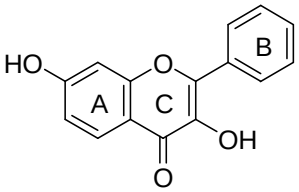


Figure 1. 7-hydroxyflavonol.

Among the flavonoids, flavonols are known for their easily formation of metal chelates because of their αhydroxy-carbonyl functional group[11]. Structural identification of flavonoids can be easily predicted by the comparison of their Ultraviolet and visible spectra and chelates with metal shows their characteristic spectral shifts[12-22]. These metal complexes of flavonoids change their biological effects and antioxidant properties[23,24].

In literature, there are several synthetic methods for the synthesis of 7-hydroxyflavonols (Figure 1), but a more effective synthetic method was established with changes in the previously reported methods[25], which results in the syntheses of various 7-hydroxyflavonol derivatives with high yields, shorter reaction time and easy in the isolation. This modification led to process research and development, which involves no intermediates like chalcones, aurones

and any other side products. There are also various modifications was done in AFO reaction [26,27]however, they are not proficient as well. They implicate steps like synthesis of chalcone and their oxidative cyclization, giving 7-hydroxyflavonol and aurone. Additionally, these reactions are time consuming with tedious workup and further purification processes for the products. This type of reactions gives products between 30-50% [28-32].

Regarding the synthesis of 7-hydroxyflavonol, reported synthetic method involved six steps, starting with 2,4-dihydroxy acetophenone and benzoyl chloride. This process requires almost 60 h for the completion [33] (Figure 2).

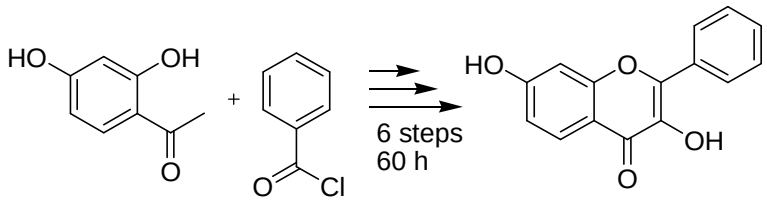


Figure 2. Literature synthesis of 7-hydroxyflavonol [33]

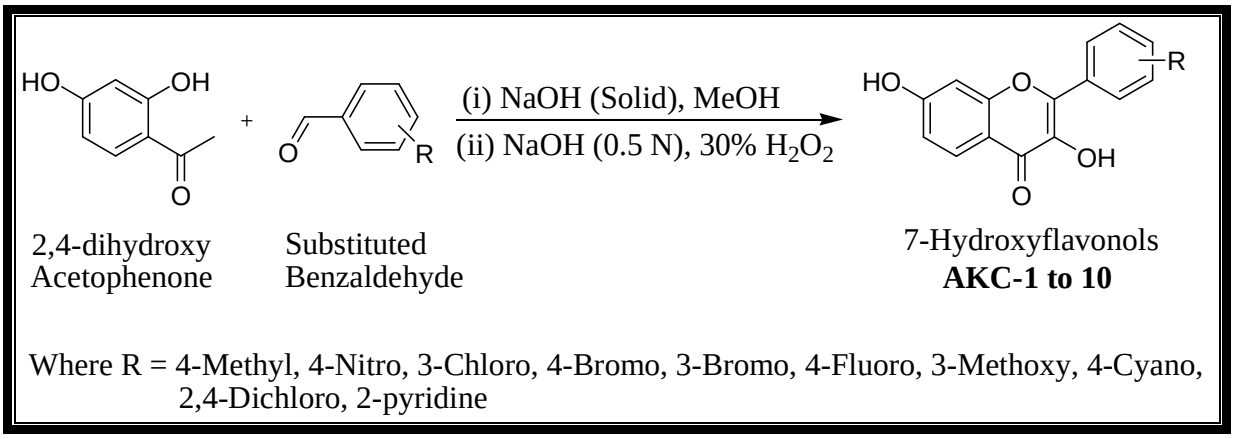
To obtain 7-hydroxyflavonols in one step, we have carried out reaction in ethanol and sodium hydroxide at reflux temperature for 5h, which was further cyclized in situ at RT with the help of 30 % hydrogen peroxide. Accordingly, Ten derivatives of 7-hydroxyflavonol were obtained in single step with high yield, by normal extraction of product, and simple recrystallization method without the requirement of any purification.

MATERIALS AND METHODS

All the reagents were purchased from Spectrochem, Aldrich and Merck and were utilized as such. Elemental analyses were recorded on aEuroVector EA 3000 elemental analyzer. Mass and IR spectra were taken with the GCMS-QP 2010 mass spectrometer andFTIR-8400spectrophotometer (Shimadzu), respectively.^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II (400 MHz)spectrometer in DMSO-d_6.Tetramethylsilane (TMS) was used as internal standard and chemical shifts were shown in δ ppm.

General procedure for 7-hydroxyflavonol syntheses

To the solution of 2,4-dihydroxyacetophenone (5 mmol) in ethanol was added solid sodium hydroxide plates (5 mmol) and stir for half an hour. After homogenous solution, substituted benzaldehyde (5 mmol) was added and refluxed until the color changed to yellow to orange (about 5 hours). The reaction was cooled to 0 ^{o}C and sodium hydroxide (0.5 N, 10 ml) and hydrogen peroxide(30%, 0.684 ml) were added. The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and after the completion of thereaction; it was poured into ice-water and acidified with the diluted hydrochloric acid. Yellow-brown precipitate was filtered and washed with water several times. The Crude product was recrystallized with ethanol. Further Purification was done with 2-propanol-hexane mixture to give final compounds AKC-1 to 10. (Scheme – 1)



Scheme 1. General Synthetic Procedure of 7-hydroxyflavonols

3,7-dihydroxy-2-p-tolyl-4H-chromen-4-one AKC-1: Yellow solid (78%), Mp: 198-200 ^{o}C. MS: *m/z* 269 $[M+1]^{+}$; analytical Calculated for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51 %; Found C, 71.61; H, 4.42 %. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.44 (3H, s, CH_3), 6.73~6.81 (2H, d, H-8,6), 7.28~7.30 (2H, d, J= 7.7 Hz, H-3',5'), 7.39~7.41 (2H, d, J= 6.7

Hz, H-2',6'), 7.60~7.62 (1H, d, J= 6.9 Hz, H-5), 9.45 (1H, s, OH-3) and 9.85 (1H, s, OH-7). ^{13}C-NMR (400 MHz, DMSO-d_6) δ169.0, 157.6, 155.9, 149.3,145.7, 137.4, 132.1, 129.1, 128.9, 124.7, 124.1, 123.2,123.1, 120.4,118.2, 97.4, 55.6, 44.6, 15.8.

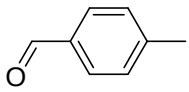
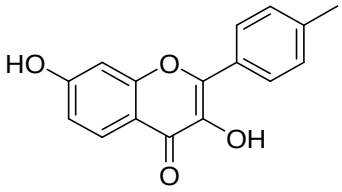
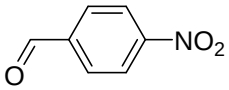
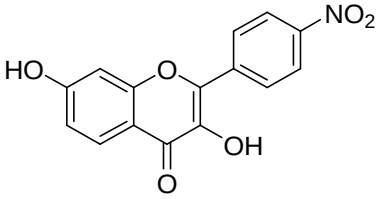
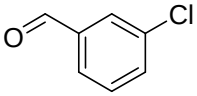
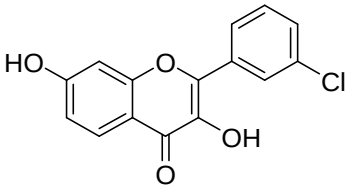
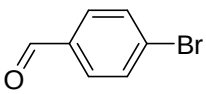
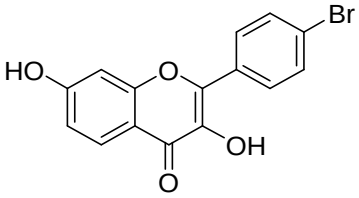
3,7-dihydroxy-2-(4-nitrophenyl)-4H-chromen-4-one AKC-2: Yellow solid (64%), Mp: 209-211 ^{o}C. MS: *m/z* 290 $[M+1]^+$; analytical Calculated for $C_{15}H_9ClO_4$: C, 62.41; H, 3.14 %; Cl, 12.28; Found C, 62.39; H, 3.25; Cl, 12.22 %. ^{1}H-NMR (400 MHz, DMSO-d_6) 6.51 (1H, s, H-8), 6.61 (1H, d, J= 8.4 Hz, H-6), 7.37 (1H, t, H-3'), 7.42 (1H, d, J = 7.6 Hz, H-4'), 7.46 (1H, d, J = 7.6 Hz, H-2'), 7.64~7.66 (2H, d, H-5,6'), 9.51 (1H, s, OH-3) and 9.74 (1H, s, OH-7). ^{13}C-NMR (400 MHz, DMSO-d_6) δ172.2, 161.5, 157.5, 146.9, 146.7, 138.2, 136.5, 129.1, 124.3, 114.7, 114.5, 102.6.

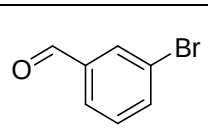
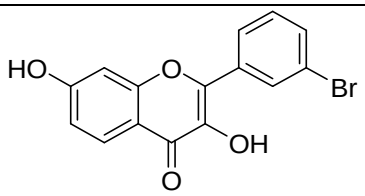
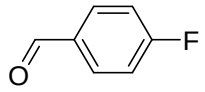
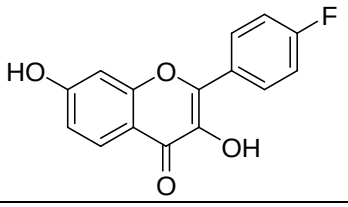
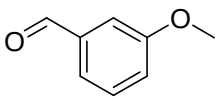
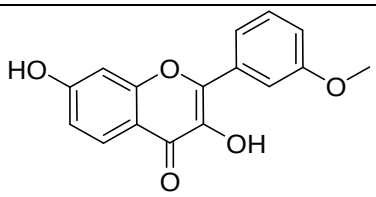
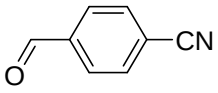
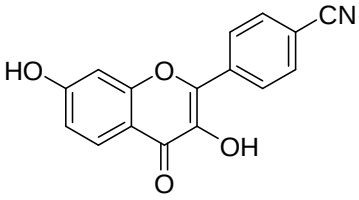
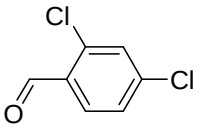
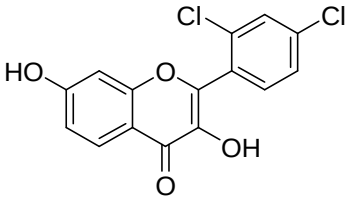
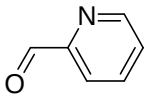
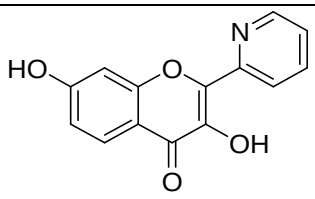
2-(3-chlorophenyl)-3,7-dihydroxy-4H-chromen-4-one AKC-3: Yellow solid (66%), Mp: 206-208 ^{o}C.MS: *m/z* 334 $[M+1]^+$; analytical Calculated for $C_{15}H_9BrO_4$: C, 54.08; H, 2.72; Br, 23.99; Found C, 54.01; H, 2.82; Br, 24.10 %. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.65 (2H, m, H-8,6), 7.39~7.41 (2H, m, H-4',5'), 7.47 (1H, d, H-6'), 7.70 (1H, s, H-2'), 7.74 (1H, d, H-5), 9.43 (1H, s, OH-3) and 9.91 (1H, s, OH-7).^{13}C-NMR (400 MHz, DMSO-d_6) δ172.2,161.5, 157.5, 147.7, 137.1, 133.2, 133.0, 129.6, 129.5, 128.8, 128.1, 127.2, 114.5, 114.7, 102.6.

2-(4-bromophenyl)-3,7-dihydroxy-4H-chromen-4-one AKC-4: Yellow solid (68%), Mp: 213-215^{o}C.MS: *m/z* 334 $[M+1]^+$; analytical Calculated for $C_{15}H_9BrO_4$: C, 54.08; H, 2.72; Br, 23.99; Found C, 53.98; H, 2.85; Br, 24.05 %. ^{1}H-NMR (400 MHz, DMSO-d_6) δ6.67~6.68 (2H, m, H-8,6), 7.43~7.45 (2H, m, H-2',6'), 7.58 (2H, d, H-3',5'), 7.67 (1H, d, H-5), 9.46 (1H, s, OH-3) and 9.83 (1H, s, OH-7). ^{13}C-NMR (400 MHz, DMSO-d_6) δ 172.2, 161.5, 157.5, 146.7, 136.5, 131.7, 129.7, 128.0, 125.9, 114.7, 114.5, 102.6.

2-(3-bromophenyl)-3,7-dihydroxy-4H-chromen-4-one AKC-5: Yellow solid (62%), Mp: 211-213^{o}C. MS: *m/z* 273 $[M+1]^+$; analytical Calculated for $C_{15}H_9FO_4$: C, 66.18; H, 3.33; F, 6.98; Found C, 66.11; H, 3.44; F, 6.93 %. ^{1}H-NMR (400 MHz, DMSO-d_6) 6.53 (1H, s, H-8), 6.56 (1H, d, J= 8.4 Hz, H-6), 7.31 (1H, t, H-5'), 7.45 (1H, d, J = 7.6 Hz, H-6'), 7.62~7.65 (2H, m, H-4',5), 7.79 (1H, s, H-2'), 9.47 (1H, s, OH-3) and 9.76 (1H, s, OH-7). ^{13}C-NMR (400 MHz, DMSO-d_6) δ 172.2, 161.5, 157.5, 147.7, 137.1, 132.6, 132.2, 131.2, 128.1, 127.5, 123.7, 114.7, 102.6.

Table 1. Synthesized 7-hydroxyflavonols[a]

Entry	Aldehydes	7HF	Yield (%)	Reaction time
1			72	5 h
2			64	5 h
3			66	5 h
4			68	4 h

5			**62**	**4 h**
6			**65**	**4 h**
7			**60**	**5 h**
8			**68**	**4 h**
9			**56**	**3 h**
10			**65**	**4 h**

[a] Experimental conditions: (i) NaOH (solid), MeOH, reflux; (ii) NaOH (0.5 N), 30 % H_2O_2. All AKC-1 to 10 were filtered after the crude product was poured into ice-water and acidified with dil.HCl.

CONCLUSION

A rapid and convenient synthetic method has been developed as compare to the previously reported methods. Numerous substituted 7-hydroxyflavonols derivatives can be made with this efficient method. This method provides the higher yield with no side product formation in comparative less reaction time and resulted 7-hydroxyflavonols can be easily isolated by simple filtration from the reaction mixture with high purity. Thus, prescribed method for the syntheses of 7-hydroxyflavonols will be beneficial than former reported synthetic methods.

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